

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
6 June 2002 (06.06.2002)

PCT

(10) International Publication Number  
**WO 02/43726 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/135**,  
A61P 25/00, C07C 13/40, 213/02

(21) International Application Number: PCT/FI01/01031

(22) International Filing Date:  
27 November 2001 (27.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
09/722,262 28 November 2000 (28.11.2000) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD FOR INDUCING COGNITION ENHANCEMENT BY USE OF TRIMETHYL-BICYCLO[2.2.1]HEPTANE DERIVATIVES

(57) Abstract: A method for inducing cognition enhancement in a mammal by administering to the mammal an effective amount of 1,7,7-trimethylbicyclo[2.2.1]heptane derivative of Formula I wherein R is hydrogen or methyl, or a pharmaceutically acceptable salt thereof.

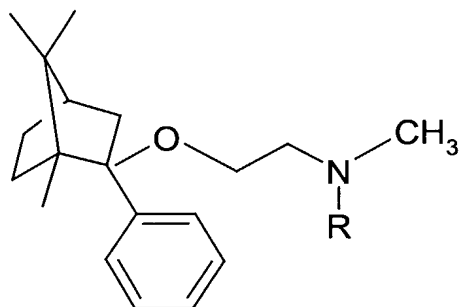


**WO 02/43726 A1**

## METHOD FOR INDUCING COGNITION ENHANCEMENT BY USE OF TRIMETHYL-BICYCLO[2.2.1]HEPTANE DERIVATIVES

## FIELD OF THE INVENTION

The present invention relates in general to a method for inducing cognition enhancement in a mammal. More particularly, the invention relates to a method for inducing cognition enhancement in a mammal by administering to the mammal an effective amount of 1,7,7-trimethylbicyclo[2.2.1]heptane derivative of Formula I



wherein R is hydrogen or methyl, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method of treating cognitive impairment in a mammal, such as, but not limited to the cognitive impairment associated with somatic diseases, psychiatric disorders and aging by administering to the mammal an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realised and attained by means of the elements and combinations particularly pointed out in the appended claims.

## BACKGROUND OF THE INVENTION

The active ingredients of this invention, (1R,2S,4R)-(-)- 2-phenyl 2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, known as deramciclane, and (1R,2S,4R)-(-)- 2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, known as N-desmethylderamciclane, and their pharmaceutically acceptable acid addition salts with inorganic and organic acids generally used for the purpose, fall within the disclosures of U.S. Patent No. 4,342,762 and International Patent Application No. WO 98/17230, respectively, which are both incorporated herein by reference.

These compounds are selective serotonin 5HT<sub>2A</sub>- and/or 5HT<sub>2C</sub>-receptor antagonists. They have shown anxiolytic-like effects in animal test models.

## DESCRIPTION OF THE INVENTION

Applicants have surprisingly discovered that the compounds of formula (I) do induce cognition enhancement in a mammal. Accordingly, an object of the present invention is a method for inducing cognition enhancement in a mammal by administering to the mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In addition, the present invention provides a method of treating cognitive impairment in a mammal associated with somatic diseases, psychiatric disorders and aging by administering to the mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. Somatic diseases, such as but not limited to dementias (e.g. Lewy body dementia, vascular dementia, Alzheimer's Disease, and HIV associated dementia) and Parkinson's Disease, are associated with serious impairment in cognitive function. Cognitive impairment is related also to several psychiatric disorders, especially to affective disorders (e.g. depression, psychotic disorders, such as schizophrenia) and anxiety disorders. Anxiety disorders include but are not limited to Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder

(OCD), Post-Traumatic Stress Disorder (PTSD), Social Anxiety Disorder (SAD), Panic Disorder (PD), agoraphobia, and Attention Deficit Hyperactivity Disorder (ADHD). In addition, cognition impairment is caused by several disorders associated with aging, such as Age Associated Memory Impairment. Further, cognitive impairment is often related to the usage of drugs, such as benzodiazepines and tricyclic antidepressants which are common in the treatment of different somatic diseases and psychiatric disorders.

For the purposes of this disclosure and claims the term “treatment” is relating to treatment in order to cure or alleviate the disease or its symptoms, and to treatment in order to prevent the development or the exacerbation of the disease or its symptoms.

Pharmaceutically acceptable salts of the compound of Formula (I) can be formed with inorganic acids, e.g. hydrohalogenic acid such as hydrochloric acid or hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid, or organic acids e.g., tartaric acid, succinic acid, malic acid, maleic acid, fumaric acid, citric acid, or lactic acid. Salt with fumaric acid is preferred.

Pharmaceutical compositions containing a compound of Formula (I) or a pharmaceutically acceptable salt thereof as the active ingredient include the usual oral dosage forms, such as tablets, capsules, and liquid preparations. In oral dosage forms, the active ingredient can be mixed with suitable pharmaceutically acceptable excipients, such as starch, lactose, sucrose and magnesium stearate, in accordance with conventional pharmaceutical practice.

The precise amount of the drug to be administered to a mammal for inducing cognition enhancement and for the treatment of cognitive impairment is dependent on numerous factors known to one skilled in the art, such as the compound to be administered, the general condition of the patient, the condition to be treated etc. For example, the usual recommended oral daily dose of deramciclane would be about 5-150 mg/day, preferably 30-60 mg/day.

The invention will be further clarified by the following example, which is intended to be purely exemplary of the invention.

#### EXAMPLE

The cognition enhancement properties of deramciclane were studied in a randomised placebo-controlled double-blind study. The subjects were randomly assigned to four parallel groups to receive one tablet twice daily (b.i.d) of a placebo, 5mg (=10mg/day), 15mg (=30mg/day), or 30mg (=60mg/day) deramciclane. The study started with a one-week placebo run-in period, followed by an eight-week placebo-controlled active treatment and a two-week placebo washout period.

The efficacy of deramciclane on cognition enhancement was studied using the cognitive part of Hamilton Anxiety Scale (HAM-A) which consists of the concentration and memory items. Cognition enhancement was also assessed using Udvalg for Kliniske Undersogelser (UKU) scale.

#### RESULTS

Administration of deramciclane improved the cognition when measured by the cognitive part of the HAM-A. This improvement was statistically significant ( $p=0.04$ , Cochran-Mantel-Haenszel statistics) in group receiving deramciclane 15 mg b.i.d when compared to placebo in the cognitive part of the HAM-A scale. The results are presented in Table 1.

In addition, when the UKU-scale was used, there was a statistically significant positive correlation in the trend analysis indicating dose-response relationship with regard to concentration difficulties. The difference between the group receiving deramciclane 15 mg b.i.d and placebo group was statistically significant ( $p=0.01$ ). The results are presented in Table 2.

Table 1.  
Hamilton Anxiety Scale/Intellectual, cognitive

	Placebo	5 mg b.i.d	15 mg b.i.d.	30 mg b.i.d.
Baseline				
Not Present	1 (2%)	3 (6%)	3 (6%)	3 (6%)
Mild	13 (26%)	17 (31%)	12 (24%)	15 (28%)
Moderate	33 (66%)	33 (61%)	35 (69%)	28 (53%)
Severe	3 (6%)	1 (2%)	1 (2%)	7 (13%)
After 8 weeks				
Not Present	12 (29%)	15 (35%)	21 (48%)	22 (48%)
Mild	20 (48%)	20 (47%)	19 (43%)	14 (30%)
Moderate	10 (24%)	6 (14%)	3 (7%)	10 (22%)
Severe	0	2 (5%)	1 (2%)	0

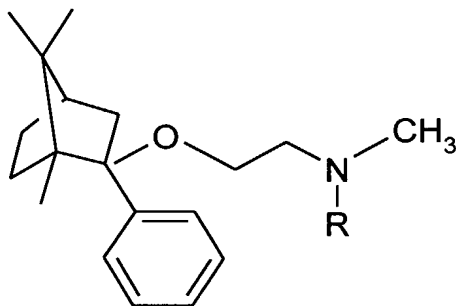
Table 2.  
UKU-scale/concentration difficulties

	Placebo	5 mg b.i.d	15 mg b.i.d.	30 mg b.i.d.
Baseline				
Normal	4 (8%)	8 (5%)	4 (8%)	3 (6%)
Mild	15 (29%)	15 (28%)	16 (30%)	16 (30%)
Moderate	28 (55%)	30 (56%)	32 (60%)	31 (57%)
Severe	4 (8%)	1 (2%)	1 (2%)	4 (7%)
After 8 weeks				
Normal	12 (29%)	15 (35%)	24 (55%)	23 (50%)
Mild	19 (45%)	19 (44%)	16 (36%)	14 (30%)
Moderate	10 (24%)	9 (21%)	3 (7%)	9 (20%)
Severe	1 (2%)	0	1 (2%)	0

Although the invention has been illustrated by the preceding example, it is not to be construed as being limited to the materials employed therein; rather, the invention is directed to the generic area as herein disclosed. Various modifications and embodiments thereof can be made without departing from the spirit or scope thereof.

## CLAIMS:

1. Use of a compound of Formula (I)

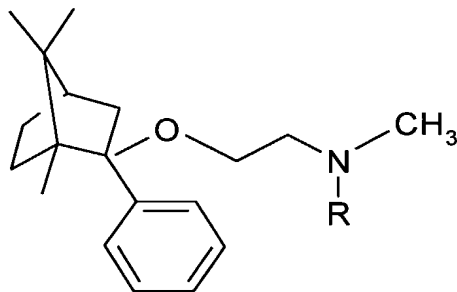


wherein R is hydrogen or methyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inducing cognition enhancement in a mammal.

2. The use of claim 1, wherein the mammal is human.
3. The use of claim 1, wherein the compound is deramciclane or a pharmaceutically acceptable salt thereof.
4. The use of claim 1, wherein the effective amount of the medicament is about 5-150 mg/day.
5. The use of claim 4, wherein the effective amount of the medicament is about 10-60 mg/day.
6. The use of claim 5, wherein the effective amount of the medicament is about 30 mg/day.



7. Use of a compound of Formula (I)



wherein R is hydrogen or methyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cognitive impairment.

8. The use of claim 7, wherein the cognitive impairment is associated with Parkinson's Disease.
9. The use of claim 7, wherein the cognitive impairment is associated with dementias.
10. The use of claim 7, wherein the cognitive impairment is associated with an anxiety disorder.
11. The use of claim 10, wherein the anxiety disorder is Generalized Anxiety Disorder.
12. The use of claim 10, wherein the anxiety disorder is Obsessive Compulsive Disorder.
13. The use of claim 10, wherein the anxiety disorder is Post-Traumatic Stress Disorder.
14. The use of claim 10, wherein the anxiety disorder is Social Anxiety Disorder.
15. The use of claim 10, wherein the anxiety disorder is Panic Disorder.
16. The use of claim 10, wherein the anxiety disorder is agoraphobia.
17. The use of claim 7 herein the cognitive impairment is associated with Age Associated Memory Impairment.

18. The use of claim 7, wherein the cognitive impairment is associated with depression.
19. The use of claim 7, wherein the cognitive impairment is associated with the usage of benzodiazepines.
20. The use of claim 7, wherein the cognitive impairment is associated with the usage of tricyclic antidepressants.
21. The use of any one of claims 7 to 20, wherein the compound is deramciclane or a pharmaceutically acceptable salt thereof.
22. The use of any one of claims 7 to 21, wherein the effective amount of the medicament is about 5-150 mg/day.
23. The use of claim 22, wherein the effective amount of the medicament is about 10-60 mg/day.
24. The use of claim 23, wherein the effective amount of the medicament is about 30 mg/day.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/FI 01/01031

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/135 A61P25/00 C07C13/40 C07C213/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 March 2002

Date of mailing of the international search report

11. 04. 2002

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/FI 01/01031

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	KANERVA H ET AL : "The single dose pharmacokinetics and safety of deramciclone in healthy male volunteers." BIOPHARMACEUTICS & DRUG DISPOSITION, vol. 20, 1999, pages 327-334, XP000937808 the whole document -----	1-17

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Information on patent family members

International Application No

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